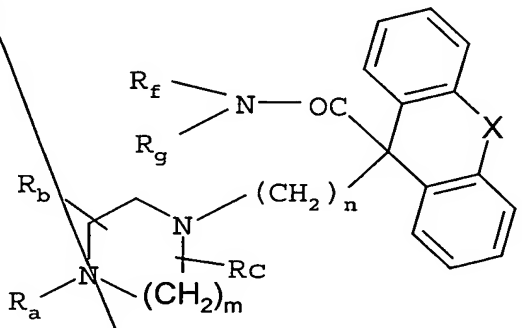
Patent Claims

1. Substituted piperazine derivatives of general formula



, (I)

wherein

n denotes the number 1, 2, 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino,

C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonyl-amino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, while the abovementioned phenyl or heteroaryl moieties of the group R_1 may be substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by a hydroxy, C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, amino-carbonyl, C_{1-3}-alkylaminocarbonyl or N,N-di-(C_{1-3}-alkyl)-aminocarbonyl group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which may be identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group,

while the tricyclic group in the abovementioned general formula I may be mono- or disubstituted by fluorine or chlorine atoms, by methyl or methoxy groups and the substituents may be identical or different,

and by the abovementioned heteroaryl groups are meant 6-membered heteroaryl groups containing one, two or three nitrogen atoms, or 5-membered heteroaryl groups which may contain one to four heteroatoms such as, for example, nitrogen, oxygen and sulphur, while hydrogen atoms bound to nitrogen may optionally be replaced by C_{1-3}-alkyl groups,

the isomers and the salts thereof.

2. Substituted piperazine derivatives of general formula I according to claim 1, wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond, an oxygen atom, a methylene, ethylene, imino or N-(C_{1-3}-alkyl)-imino group,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy group, a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a phenoxy, heteroaryloxy, phenyl-C_{1-3}-alkoxy, carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, nitro, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, phenyl-C_{1-3}-alkyl-amino, N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino, C_{1-3}-alkylcarbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, C_{1-3}-alkylsulphonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkylsulphonylamino group, while the abovementioned phenyl or heteroaryl moieties of the group R_1 may be substituted by one to five fluorine, chlorine or bromine atoms, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a hydroxy

group, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, and

R_2 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or a C_{1-4}-alkoxy group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

R_1 and R_2 together represent a methylenedioxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl or monocyclic heteroaryl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by a fluorine, chlorine or bromine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by a hydroxy, or C_{1-3}-alkoxy group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f and R_g, which may be identical or different, denote hydrogen atoms, C_{1-6}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, C_{3-7}-cycloalkyl groups, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl groups, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or

by a carboxy, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylaminocarbonyl, N,N-di-(C_{1-3}-alkyl)-aminocarbonyl, N,N-di-(C_{1-3}-alkyl)-amino, nitro or amino group, or

R_f and R_g together with the nitrogen atom between them denote a 3- to 7-membered cycloalkyleneimino group, while the methylene group in the 4 position of a 6- or 7-membered cycloalkyleneimino group may additionally be replaced by an oxygen or sulphur atom, by a sulphinyl, sulphonyl, imino or N-(C_{1-3}-alkyl)-imino group,

the isomers and the salts thereof.

3. Substituted piperazine derivatives of general formula I according to claim 1, wherein

n denotes the number 3, 4 or 5,

m denotes the number 2 or 3,

X denotes a carbon-carbon bond or an oxygen atom,

R_a is defined as in claim 2, and

R_b and R_c independently of one another denote a hydrogen atom or a methyl group and

R_f denotes a hydrogen atom, a C_{1-6}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a C_{3-7}-cycloalkyl group, phenyl, heteroaryl, phenyl-C_{1-3}-alkyl or heteroaryl-C_{1-3}-alkyl group, while the abovementioned phenyl groups and heteroaryl groups may in each case be substituted by one to three fluorine, chlorine or

bromine atoms, by one to three C_{1-3}-alkyl groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, by one to three hydroxy groups, one to three C_{1-3}-alkoxy groups wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, or by a nitro or amino group, and

R_g denotes a hydrogen atom,

the isomers and the salts thereof.

4. Substituted piperazine derivatives of general formula I according to claim 1, wherein

n denotes the number 4,
m denotes the number 2,

X denotes a carbon-carbon bond or an oxygen atom,

R_a denotes a phenyl group or heteroaryl group substituted by the groups R_1 and R_2, wherein

R_1 denotes a hydrogen, fluorine or chlorine atom, a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a C_{1-4}-alkoxy group, a phenoxy group, a phenyl-C_{1-3}-alkoxy or a nitro or amino group,

wherein the abovementioned phenyl moiety of the phenoxy group may be substituted by a chlorine atom or by a methoxy group,

R_2 denotes a hydrogen atom, a chlorine atom or a C_1-C_4-alkoxy group,

or R_a denotes a monocyclic heteroaryl or phenyl group which is substituted in each case by a phenyl group,

R_b and R_c independently of one another denote a hydrogen atom or a C_{1-3}-alkyl group and

R_f denotes a C_1-C_6-alkyl group wherein the hydrogen atoms may be wholly or partly replaced by fluorine atoms, a phenyl-C_{1-3}-alkyl group, while the abovementioned phenyl group may be substituted in each case by a fluorine atom or by a C_1-C_3-alkoxy group, and

R_g denotes a hydrogen atom,

the isomers and the salts thereof.

5. The following substituted piperazine derivatives of general formula I according to claim 1:

(a) 9-[4-(4-biphenyl-3-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide and

(b) 9-[4-(4-biphenyl-4-yl-piperazin-1-yl)-butyl]-9H-fluorene-9-carboxylic acid-(2,2,2-trifluoroethyl)-amide,

the isomers and the salts thereof.

6. Physiologically acceptable salts of the compounds according to claims 1 to 5.

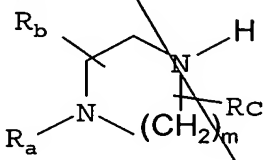
7. Medicaments, containing a compound according to at least one of claims 1 to 5 or a salt according to claim 6 optionally together with one or more inert carriers and/or diluents.

8. Use of a compound according to at least one of claims 1 to 5 or a salt according to claim 6 for the preparation of a medicament having a lowering effect on the plasma levels of atherogenic lipoproteins.

9. Process for preparing a medicament according to claim 6, characterised in that a compound according to at least one of claims 1 to 4 or a salt according to claim 5 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

10. Process for preparing the compounds according to claims 1 to 6, characterised in that

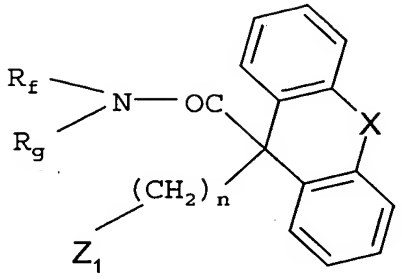
a. a compound of general formula



, (II)

wherein

R_a, R_b and R_c are defined as in claims 1 to 4, is reacted with a compound of general formula



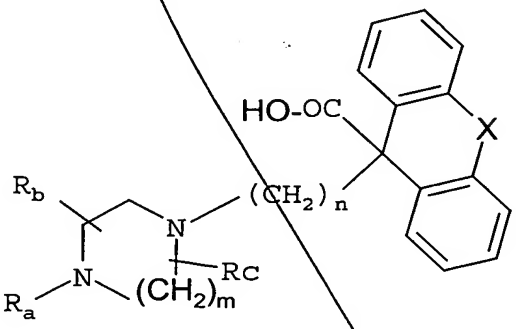
, (III)

wherein

n, R_f, R_g and the tricyclic system are defined as in claims 1 to 4 and

Z_1 denotes a nucleofugic leaving group, or

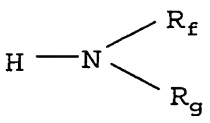
b. a compound of general formula



, (IV)

wherein

the tricyclic system is defined as in claims 1 to 4, is reacted with an amine of general formula



, (V)

wherein
R_f and R_g are defined as in claims 1 to 4, or with the reactive derivatives thereof and

if desired a compound of general formula I thus obtained which contains a nitro group is converted by reduction into a corresponding amino compound and/or

a compound of general formula I thus obtained wherein R_f denotes a hydrogen atom is converted by alkylation into a corresponding compound wherein R_f denotes a C_{1-3}-alkyl or phenyl-C_{1-3}-alkyl group, and/or

any protecting group using to protect reactive groups during the reactions is cleaved and/or

a compound of general formula I thus obtained is resolved into its stereoisomers and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with an inorganic or organic acid or base.

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